[Copeman, Sydney Monckton]
Report on diphtheria

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ON

PUBLIC HEALTH AND MEDICAL SUBJECTS.

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Dr. COPEMAN'S REPORT ON DIPHTHERIA.

PRELIMINARY NOTE TO THE CHIEF MEDICAL OFFICER, SIR GEORGE NEWMAN, K.C.B., M.D.

I.—Schick Test and Active Immunisation against Diphtheria.

The report herewith submitted deals, *inter alia*, with the use of the Schick test as a means of recognising susceptibility to diphtheria, and with the method of conferring immunity, by means of inoculations of a standardised toxin-antitoxin mixture, on those who have been found to be susceptible to diphtheria by this test, or are assumed to be susceptible on other grounds. This system of diphtheria prevention has been adopted on an extensive scale in New York, where prevalence of diphtheria has been greater and the mortality from this disease considerably higher than in this country. The object of its adoption is not the separation from the population of infective cases and carriers; it is assumed that risk of infection from such cases must always be considerable and to a large extent beyond control, and it is consequently considered preferable to adopt a method which secures a substantial immunity of the general population concerned, or at least of a large part of it. In order that this may be obtained on a sufficient scale, the New York system provides a medical service for carrying out the testing and immunising, especially in the school population. Steps are also taken to obtain the co-operation of medical practitioners who apply the Schick test, and where necessary undertake the immunisation, with material supplied to them from the New York State laboratories.

In his report Dr. Copeman has collected and set out some of the principal considerations and data regarding the Schick test and methods of immunising against diphtheria. With this he has combined the results of personal observations of these methods from his experience at Bristol and that of several collaborators, particularly Dr. D. S. Davies, Professor Walker Hall, Dr. Nixon and Dr. Norgate at Bristol, and Dr. O'Brien of the Wellcome Laboratories.

The observations on this subject in the report will, it is anticipated, be useful to Medical Officers of Health and Hospital and School Medical Officers who have specially to deal with diphtheria outbreaks in this country. It would be premature to advise that in English communities general immunisation of persons susceptible to diphtheria should be attempted on the New York scale. More information and experience would be necessary before this could be recommended, and it would be necessary to be satisfied that equally good results cannot be obtained by extension and improvement of the methods of

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diphtheria prevention on which we rely at present. At the same time, there are already circumstances in which the evidence available may be considered to warrant a trial of the Schick reaction and toxin-antitoxin immunisation. For example, a parent who for one or another cause is specially anxious that his child should avoid all possible risk of contracting diphtheria, may ask whether medical science cannot now provide a means by which the degree of the child's susceptibility can be estimated, and by which, if the susceptibility is great, the child can be protected for at least some years without any substantial risk, and with at most only a transient and insignificant disturbance of health, as the result of the inoculation. A similar question may be asked by nurses and others likely to come much into contact with diphtheria cases, or again by Medical Officers of residential schools and other limited communities at a time when diphtheria is epidemic. The information now available—much of which is epitomised in Dr. Copeman's Report—shows that there is good warrant for an affirmative answer to such questions.

The technique of the Schick test is comparatively simple, though, like all scientific methods, it requires some little experience before the observer can have confidence in himself and in his interpretation of the reactions obtained. Its essential points are now fully described in medical literature and some practical suggestions—especially as to control inoculations with heated toxin—are set out in this report. Demonstrations of the test might readily be given (if they are not given already) at post-graduate courses or during the instruction on infectious diseases which forms part of the curriculum of medical students.

The immunising treatment is obtained by a series of simple inoculations. The necessary toxin-antitoxin mixture (as also the toxin required for the Schick test) is, in New York, distributed on a large scale from State and other recognised laboratories, the authorities of which guarantee the uniformity of the constituent elements and of the mixture. Corresponding supplies in this country have hitherto been obtainable from the Wellcome Laboratory, and no doubt bacteriologists at other laboratories who are experienced in this type of work can furnish the protective material prepared according to the generally accepted standards. No officially standardised supply is issued by our public authorities.

It is important to note that the constitutional reaction produced by the immunising mixture may exceptionally be somewhat severe, particularly in adults and in those who, in response to the Schick test, show a positive combined with a strong " pseudo " reaction. Dr. Copeman's experience in this matter is referred to on pages 22 and 23 of his report. This consideration, however, need not prevent the use of the immunisation method, especially when regard is had to the much more formidable results of an attack of diphtheria. But, in the adult especially, it is advisable to meet the possibility by commencing inoculation

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with a minimal dose—say, 0·01 c.c.—which is unlikely to cause any trouble even in susceptible individuals.

II.—Customary Methods of Control of Diphtheria.

Dr. Copeman also makes some observations in his report on the general question of dealing with diphtheria carriers and on other matters which bear on the methods of control of diphtheria which are customary in this country.

This question has recently received much attention from various sides, particularly in consequence of the increased epidemicity of diphtheria in certain districts of England, including London, during the past few years. In connection with this the Medical Officers concerned with the matter at the Ministry have had the benefit of frequent exchange of views with Medical Officers of Health, Medical Officers of infectious diseases hospitals, and bacteriologists, including members of the Committee of the Medical Research Council which is studying bacteriological standards, and a committee of the Epidemiological Section of the Royal Society of Medicine.

In essence, the chief difficulty in the choice of appropriate methods of prevention lies in assessing the infective ability of the different individuals who collectively are classed as " carriers " of the diphtheria bacillus. The fact that this bacillus, when present in the mucous membrance of throat or nose, can be recovered and identified by swabbing and transmitting the swab to the bacteriologist, was established many years ago; first for those suffering from clinical diphtheria, and afterwards for the convalescent and for the healthy person who harbours the bacillus for longer or shorter periods without any ill results to himself. In its original medical application, and in methods of public health administration based upon it, the simple procedure of swabbing and awaiting a positive or negative opinion from a bacteriologist seemed almost self-sufficient. The bacteriologist's report on the swab determined the diagnosis of the case; persons believed to have been closely in contact with the case were also swabbed; a negative finding could be considered as for practical purposes evidence of absence of danger, while any positive finding demanded all available precautions, time, and patience, until at length one or more reports on subsequent swabs happily proved to be negative.

These earlier and simpler conceptions have now in large measure been abandoned with the growth of knowledge as to the frequency of the carrier condition (in other diseases as well as in diphtheria) and of the very definite distinction which we have now to make between virulent and non-virulent diphtheria bacilli, although these are morphologically and culturally indistinguishable. Moreover, it is generally realised that, in practice, the results of swabbing are materially affected both by the thoroughness of the swabbing itself and by the method of examination and reporting which is followed in the laboratory. In all these

circumstances it is important not to attach undue importance to a ritual of routine bacteriological examinations and reports, and not to regard such examinations and reports (as usually obtained in present practice) as the one and only basis of preventive action against diphtheria.

Observations may here be made on the following points, which frequently arise one way or another in practice.

(a) *Notifiable Diphtheria.* — The notification of cases of diphtheria under the Infectious Diseases (Notification) Acts should be limited to persons actually suffering from diphtheria, *i.e.*, those exhibiting clinical signs of the disease, with or without bacteriological evidence of the presence of diphtheria bacilli. In the practice of some districts and of many medical practitioners, including, often, the medical officers of hospitals and residential schools, notification is frequently extended to include diphtheria carriers who themselves present no sign of illness. It is doubtful whether this practice is justifiable. Statistically it leads to much confusion; indeed, comparisons between diphtheria notification rates in different areas and in different parts of the country have for some years been rendered very unreliable by reason of uncertainty in this respect. Administratively, the effect may be equally unsatisfactory. The healthy carrier, as a result of his notification as a victim of diphtheria, is frequently removed to hospital where he may stay to the exclusion of persons urgently requiring treatment (a matter of great importance during the stress of an epidemic) and at unnecessary cost to the public authorities. Further enquiry and consideration might have shown that no benefit to the community or to the individual was likely to result from his segregation. A child attending school, for example, who is found to be a carrier, may merely have acquired that condition in common with the majority of the other children in his class at a time when diphtheria infection has been prevalent in the school for many months, and himself have no signs of illness; his bacilli may be non-virulent, and consequently he does not in all probability constitute a danger to others. Non-virulent diphtheria bacilli are not known to be capable of changing into virulent organisms.

It is no doubt of assistance to the Medical Officer of Health, as a guide to preventive measures, to be informed of the result of the swabbing of any person in his district who is suspected to have diphtheria or to be a diphtheria carrier. But as the notification of cases which do not present clinical evidence of diphtheria cannot be required under the Infectious Diseases (Notification) Acts, arrangements should be made to obtain information in regard to such cases without relying upon the machinery of notification. Any local authority may incur necessary expenditure in arranging with practitioners in the district for the supply of such information relating to carriers as may be needed to enable the authority and its officers to carry out their duties under the Public Health Acts.

(b) *Antitoxin Treatment.*—Attention should be called to one circumstance in which substantial danger may result from depending too exclusively on bacteriological results. This is the case of antitoxin treatment, which should be begun at once when the clinical evidence of diphtheria is definite. Dr. F. Thomson and other experienced medical officers have recently insisted on the unsatisfactory results of the delay which is caused by the medical attendant having waited for a report on swabs sent to the bacteriologist, before administering antitoxin.

(c) *Fitness for Discharge from Hospital.*—There is considerable divergence in the practice of different infectious disease hospitals as to the extent to which diphtheria convalescents are bacteriologically examined before being sent to their homes. If abundance of bacteriological assistance were available, including ample opportunities for applying tests for virulence, it would no doubt be desirable to follow a general rule that no case should be discharged until a sufficient number of examinations has been made to establish a very high degree of probability that the convalescent has ceased to harbour diphtheria bacilli; or that, if he is still a carrier, the organisms concerned are non-virulent. In practice, however, these conditions can seldom be realised, and the choice lies between obtaining a much more imperfect degree of information from routine swabbing, without virulence tests, and discharging the ordinary cases, when clinically convalescent, without any appeal to bacteriological findings.

There is little doubt that the necessity for routine bacteriological examinations can be materially lessened by due attention to the re-establishment of normal conditions in the throat and nose before the patient is discharged. The removal of enlarged tonsils, adenoids, &c., has been shown to be of particular importance and to form in itself a powerful method of reducing the numbers of infective carrier cases after diphtheria.

The experience in regard to return cases of certain Metropolitan Asylums Board hospitals in which no routine bacteriological examinations of discharged convalescents are made, seems to show that the return of convalescents to their homes in an infectious condition may be avoided with as much success as that obtained by those hospitals which adopt the rule that two or more negative swabbings must be obtained before the discharge of the patient is permitted.

In general, perhaps, it may be advised that when the bacteriological resources at the disposal of a hospital are limited, they will best be utilised for purposes of diagnosis of doubtful cases, and, with regard to convalescents, for those showing chronic nasal discharge or chronic sore-throat, the nature of which requires special investigation from the carrier point of view. In such instances it is always desirable that the laboratory should be in a position to follow up any positive results by virulence tests. Some recently suggested methods for simplifying these tests are referred to by Dr. Copeman on page 29.

(d) *Return of Diphtheria Convalescents to School.*—Somewhat similar considerations here apply. The risk of return of a virulent carrier may be greatly lessened, without recourse to bacteriological tests, by making sure that the convalescent is clinically recovered, is free from nasal discharge, and has a normal throat. Exceptional instances are on record of healthy persons with apparently normal throats and no nasal discharge acting for long periods of time as carriers, and some degree of security against these rare cases may be obtained by the routine swabbing recommended in the Memorandum on Exclusion from School, 1909, which requires negative reports from three successive swabs taken on separate days as a condition of the return of the child. But even this proceeding cannot be relied upon for the certain and automatic detection of such cases, and, as already indicated, a positive result may only mean the presence of a non-virulent bacillus, which does not justify exclusion from school. In Prussia such considerations as these have led to the arbitrary solution that, for the present, no diphtheria carrier, if otherwise healthy, is to be excluded from school longer than eight weeks after clinical recovery (Ministerial Circular of 11th April 1921).

(e) *Routine Swabbing in Outbreaks of Diphtheria in Schools and Institutions.*—This practice would seem to be chiefly useful on the first appearance of cases of diphtheria in the school or class. A class, the members of which have been but slightly exposed to an initial infection, may, by means of swabbing, be pronounced with reasonable confidence to be free from carriers. Or the system may succeed in detecting one or more other children whose throats or noses are infected and so lead to their isolation and the clearing of the class, for the time being, from all carriers. At a later stage, however, and particularly in day schools, it would seem that the spread of the carrier condition (as distinct from actual diphtheria) often becomes extensive, and at this stage systematic swabbing, producing large numbers of positive results, affords little guide for useful practical action. Negative bacteriological results in such cases may be consistent with intermittences in a chronic carrier condition. In such circumstances it seems better to concentrate on the clinical condition of the children, and the temporary exclusion from school of those showing signs of chronic sore-throat and nasal discharge, while at the same time using bacteriological methods principally for the determination of the nature of these particular cases. The practice in the London County Council schools has now come to be based largely on these considerations.

Numerous observations are being made on questions such as those on which I have touched. It is to be hoped that, by their active continuance both in the laboratory and in the field, it may before long be possible to obtain scientific authority for

something like a definite code for the effective prevention of the spread of diphtheria, such, for example, as we may be said now to possess in the case of enteric fever or small-pox. At the Ministry every effort is being made to follow the development of the subject. Medical Officers of Health and Medical Officers of Schools and Isolation Hospitals can, in this connection, do a specially valuable service if they will communicate to the Ministry, in the form of special reports or otherwise, the results of preventive measures which they test, and the views which they have been able to form in regard either to the extension or to the simplification of the methods of which they have had experience.

G. S. BUCHANAN.

November 1921.

A REPORT ON CERTAIN PROPHYLACTIC MEASURES AGAINST DIPHTHERIA, BASED ON RECENT AMERICAN WORK AND ON THE INVESTIGATION OF AN OUTBREAK OF DIPHTHERIA AT THE SOUTHMEAD INFIRMARY, BRISTOL.

By S. Monckton Copeman, M.D., F.R.S.

In January of the present year the Ministry received a communication from Dr. R. H. Norgate, the Medical Superintendent of the Southmead Infirmary of the Bristol Union, reporting the occurrence of an outbreak of diphtheria in the children's ward of that institution in circumstances which seemed to call for special investigation of the conditions under which the disease was spreading.

In course of an enquiry which was consequently undertaken at that institution and afterwards at the Downend Homes and Headquarter Homes of the Bristol Union, occasion arose to utilise the Schick reaction and to immunise certain of the susceptible children by toxin-antitoxin inoculation. This was done under my general direction after communication between the Ministry and the Bristol Guardians, who, in this and other matters, afforded every facility for the enquiry. I had also the advantage of close co-operation with Dr. D. S. Davies, the Medical Officer of Health of the City, and his staff, Dr. Nixon, Physician to the Bristol Infirmary, and Dr. Norgate, the Medical Superintendent of the Infirmary, and of consultation with Professor Walker Hall regarding the bacteriological examinations in connection with these cases which were made at the Pathological Laboratory of the Bristol University.

The original outbreak which occurred at the Southmead Infirmary in January affected 15 children, five of whom died. A further series of 34 cases, apparently of independent origin, occurred subsequently at the Headquarter and Downend Cottage Homes, but fortunately none of these terminated fatally. In addition four members of the nursing staff suffered from mild attacks.

The origin and spread of the outbreak was made the subject of a very close investigation, and the various measures taken by the medical officers concerned to deal with it were in all respects satisfactory. In general, however, there were no very exceptional features which need be described in the present report, but the investigation led to the consideration of a number of questions relating to methods of prevention of diphtheria which appear to be of general interest and application, and are set out under the following headings :—

I. Notes, principally from American sources, on the Schick reaction and toxin-antitoxin immunity.

II. Technique of the Schick test, and factors influencing its reliability.

III. Active immunisation against diphtheria.
IV. Observations on diphtheria carriers.
Appendix 1.—New York recommendation as to the practical application of the Schick test.
Appendix 2.—Methods of carrying out experimental tests for virulence of diphtheria organisms.

I.—NOTES, PRINCIPALLY FROM AMERICAN SOURCES, ON THE SCHICK REACTION AND TOXIN ANTITOXIN IMMUNITY.

Recent investigations, more particularly in America, have resulted in the initiation of what appear likely to prove important advances in regard to methods employed in the prophylaxis of diphtheria, in the estimation of susceptibility to attack, as also of pathogenicity of the specific micro-organism in relation to the question of the administrative treatment of "carriers."

Immunity and Prophylaxis.—Of outstanding importance is the question of the possibility of successfully immunising susceptible individuals, especially children, against attack by the disease. Investigations by Schick and others have shown that the newly-born infant, almost invariably, is found to be naturally immune—such immunity being derived from the mother, and becoming gradually less in degree after the first few months of life. Thus, by means of the special test devised by him (of which a description is given later, *see* p. 12), Schick* found positive reactions (indicating susceptibility to the disease) in not more than 7 per cent. of the newborn, the numbers mounting, however, to 43 per cent. during the second six months of life, and to 60 per cent. between the ages of one and five years, thereafter falling again to 50 per cent. between five and fifteen years.

As a further outcome of work in this direction, it has been inferred that a considerable number of individuals retain their natural immunity throughout life. The identification of these persons therefore becomes a matter of importance in connection with any attempt at the immunisation of a community in presence of, or in anticipation of, an outbreak of the disease. By applying Schick's test, it is claimed that this information immediately becomes available, and that, consequently, passive immunisation with antitoxin (or active immunisation with a mixture of toxin and antitoxin) of a large number of individuals can be omitted, thus economising in time, labour, and expense.

In the light of experience of the working of the Vaccination Acts in this country it is clear that, even if considered desirable, no attempt at a general immunisation of the infant population would be feasible. On the other hand, in the case of certain

* Schick's original paper appeared in the Münchener Medizinische Wochenschrift, 1913, ix, 2608–2610.

institutions such as schools, the method appears capable of affording results of the utmost value and importance.

The feasibility of the adoption of this method has been discussed by Dr. Faris, who, in the *New Zealand Medical Journal* (December 1919), raises the question as to what can be done to eliminate diphtheria from an institution in which are collected together an assemblage of susceptible children. In addition to isolating detected "carriers" until three negative swabs had been obtained, it would also be necessary, so far as possible, to protect the remainder of the inmates from the risk of an attack of diphtheria. To this end alternative methods of procedure are available: either to give each child a prophylactic injection of anti-diphtheritic serum and so ensure a period of immuuity varying from three to four weeks; or, by means of the Schick test, to ascertain which children are susceptible, and then to immunise them by a series of injections of a toxin-antitoxin mixture, and thus confer on them an immunity likely to persist for a period of at least several years. The first method of administering to each child a prophylactic dose of anti-diphtheritic serum, is, he points out, one which should be used with great caution, as the period of immunity bestowed is short, while there is, among those protected, the possible risk of anaphylaxis, should it again be necessary to inject anti-diphtheritic serum in the course of an actual attack of the disease. Owing to the above-mentioned disadvantages which are attendant on this method of protection, it is not to be recommended as a routine public health measure, and it has been replaced in America by the toxin-antitoxin method.

Toxin-antitoxin Inoculations against Diphtheria. — The technique of this method of immunisation is described by Park and Williams (*Pathogenic Micro-organisms*, 1920, p. 353) as follows:—

"The mixtures of toxin-antitoxin used for immunisation contain about 2 L + doses* of toxin to each c.c. and are either neutral (66–70 per cent. L + to each unit of antitoxin) or slightly toxic (80–90 per cent. L + to each unit of antitoxin) to the guinea-pig. The dose has varied from 0·5 c.c. to 1·0 c.c., and the number of injections from one to three. The injections are made subcutaneously at intervals of seven days. The local reactions at the site of injection are generally mild; in the older children and adults redness and swelling are usually more marked. General symptoms of malaise, with a temperature of 100° to 102° F., were noted in 10 to 20 per cent. of the cases; in a few the temperature reached 104° F. The symptoms generally last from 24 to 48 hours, and then rapidly subside. Both local and general symptoms were especially evident in some of those who

* L + dose = the minimum amount of toxin which, injected together with one unit of antitoxin, will kill a guinea-pig weighing 250 grams in five days.

showed a susceptibility to the protein by giving a combined "pseudo" and true Schick reaction. No harmful after-effects were noted except that in certain cases superficial abscesses developed. All made a good recovery.

"The best results were obtained with the full immunisation, consisting of three injections of 1 c.c. each, given at weekly intervals.* The duration of the active immunity was studied in a group of children followed up for over three and a half years; these cases indicating that the active immunity persisted for at least that length of time."

The Schick Test.—This is a convenient clinical test by which the antitoxic immunity of individuals to diphtheria and consequently their susceptibility, or otherwise to the disease, can be determined. It consists of injecting intradermally into the flexor surface of the forearm a fresh solution of diphtheria toxin prepared so that 0·1 c.c. or 0·2 c.c. represents $\frac{1}{50}$ M.L.D. (minumum lethal dose) for a 250-gram guinea-pig. A 1 c.c. record syringe graduated in tenths, with a fine steel or platinum-iridium needle is to be recommended. The insertion of the needle into the proper layer of the skin is of the greatest importance, and requires a certain amount of practice to enable one to carry out the procedure smoothly. The result of the tests should be observed 24, 48, 72 and 96 hours afterwards. The reaction appears at the site of injection as a positive, negative, pseudo, or combined positive and pseudo reaction. The *positive reaction* indicated by a roughly circular area of a deep red colour around the site of injection, is due to the irritant action of the toxin acting upon tissue-cells which are not protected by antitoxin. A positive reaction indicates, therefore, that no antitoxin exists in the patient's blood, and that, in consequence, there is an absence of immunity to diphtheria. The extent of local reaction varies with the relative susceptibility of the individual.

As a result of a large number of Schick tests performed by Dr. W. H. Park among children in the various institutions in New York City, he found susceptibility to diphtheria present in about the following proportions :—

Age.	Percentage Susceptible.
Under 3 months	15
3 to 6 months	30
6 months to 1 year	60
1 to 2 years	70
2 to 3 years	60
3 to 5 years	40

* Animal experiments have afforded demonstration of the fact that the effects of a single immunising dose may not be evidenced for a period of as long as 60 days; and that even after this lapse of time, immunity is only afforded to a comparatively small extent. But the super-imposed effect of a second and of a third dose is, in each instance, enormously to increase the extent of the immunity originally produced.

Age.	Percentage Susceptible.
5 to 10 years	30
10 to 20 years	20
Over 20 years	15

These figures, which agree generally with those of Schick, indicate that the percentage of individuals susceptible to diphtheria is greatest between the ages of six months and about four years.

In the *negative* reaction there is no change at the site of injection, and a result of this kind indicates an immunity to diphtheria if the toxin used in the test is of full strength and has been freshly diluted, and the injection is made into the proper layer of the skin. It is stated by Dr. W. H. Park and Dr. Abraham Zingher that a " negative reaction in a child that has reached the age of three years indicates that it has an immunity which is probably permanent."

The fact that a " *pseudo* " reaction may occur adds to the difficulty of reading the results, although, by experience, the difficulty in distinguishing between the true and the pseudo reaction is greatly lessened. The pseudo reaction probably represents a local anaphylactic response of the tissue cells to the protein substance of the autolysed diphtheria bacilli, which is present in the toxic broth used for the test.

According to Von Behring and Kleinschmidt, the pseudo reaction shows varying degrees of infiltration, and appears as a small central area of deep red colour with a secondary areola which shades off gradually into the surrounding skin. In common with certain other observers, however, Dr. Nixon and I found at Bristol that the pseudo reaction may, on occasion, be of uniform redness, and even more extensive than the true positive reaction.

Lastly, mention must be made of the *combined reaction* which presents the elements of both the positive and the pseudo reaction in the same individual. In this case the central red area is distinctly defined, and the infiltration is well-marked. This reaction is recognised by the fact that the pseudo element disappears early, leaving persistent evidence of the true positive reaction.

To sum up, one may say that there is undoubted evidence that persons giving a negative Schick reaction are relatively immune to diphtheria. On the other hand, the fact that persons giving a positive reaction may occasionally harbour diphtheria bacilli in their throats without developing clinical diphtheria points to a form of immunity independent of the presence of natural antitoxin.

Further testimony as to the value of the Schick test has recently been forthcoming. Blum (*American J. of Dis. Child.*, July 1920) has made important observations in a large home

for infants where diphtheria had been endemic as late as 1915. When it was ascertained by the Schick test that 37 per cent. of the inmates were susceptible to the disease, attempts were made to establish an immunity in this group by means of toxin-antitoxin inoculations. It would appear that this was accomplished through injection of those susceptible, as the institution is stated to have been rendered diphtheria-free during the last five years.

Changes in the Schick reaction from negative to positive during the first three years of life, owing to the loss of congenital immunity, were found by Blum to be sufficiently numerous to justify re-testing, at least in large institutions, during this period, at intervals of a few months. According to Schick, in order to prevent the appearance of the reaction at least 1/30th unit of antitoxin per c.c. of blood is required. This amount he considers sufficient to protect against diphtheria. Von Behring states that even so small an amount as 1/100th unit of antitoxin will protect against diphtheria in uncomplicated cases.

The Schick reaction has also been used to determine the duration of passive immunity after a prophylactic dose of anti-diphtheritic serum. This was found to vary in the great majority of cases from 21 to 25 days. The effect of a previous dose of antitoxin upon the duration of passive immunity, as given by a second dose of antitoxin, can also be studied by the Schick reaction.

The Schick reaction can also be applied with advantage in testing the patients, resident staff, and nurses of infectious diseases hospitals. By its use a considerable saving of antitoxin can be effected during outbreaks of diphtheria in institutions or in homes; it relieves the fear of infection and also avoids unnecessarily sensitising individuals already immune. It might with advantage be applied in some circumstances both in the measles and the scarlet fever wards of hospitals, the value of such a method being indicated by Park, who states that of 400 cases of scarlet fever isolated in a hospital for infectious diseases, showing a negative Schick reaction and consequently receiving no immunising dose of antitoxin, not one developed clinical diphtheria, although many of them were " carriers " of virulent diphtheria bacilli. Similarly in the scarlet fever pavilion of the Willard Parker Hospital, New York, 1,200 patients were tested, and of these 556, or 46·3 per cent., gave a negative reaction. Although the negatively reacting patients were in contact with cases of diphtheria developing amongst the Schick positives, none developed clinical diphtheria, though 20 per cent. became temporary carriers of diphtheria bacilli—in many instances of virulent type.

II.—TECHNIQUE OF THE SCHICK TEST AND FACTORS INFLUENCING ITS RELIABILITY.

In order to obtain entirely satisfactory results in the carrying out of the Schick test, it is essential that certain conditions should be strictly observed.

These have reference more particularly to :—

(1) The use of a standard toxin of definite strength.
(2) The correctness of the technique.
(3) The correct interpretation of the results obtained.

(1) *Standard Toxin.*—Reference has already been made to the fact that, according to Schick's original standard, the amount of toxin to be employed represented 1/50 of the minimal lethal dose for a 250-gram guinea-pig, in 0·1 c.c. of normal saline solution. As Zingher has pointed out, however, 1/50 M.L.D. in 0·2 c.c. of saline solution is an amount which is more easily handled, and which will give rise to a small definite whitish weal-like swelling which, as the result of the injection, appears above the surface of the skin, thus indicating successful accomplishment of the operation.

This particular dilution of toxin is that which is now in general use, an additional reason for its adoption being found in the fact that reactions obtained in susceptible individuals with this dilution of toxin tend to be less severe and persistent than when the more concentrated dilution, as originally suggested by Schick, is employed. It is important to note, however, that although toxin probably retains its potency for at least six months if stored, undiluted, in a cold chamber, it should not, as a matter of routine, be used later than 24 hours after dilution.

As the outcome of the many thousand tests that have now been carried out under the direction of the New York State Department of Health, it is stated that, when made with a standard and carefully prepared dilution of the toxin, the intracutaneous injection of the small dose of diphtheria toxin necessary to the performance of the Schick test is perfectly harmless.

In certain instances in this country which have come to our notice, insufficient attention appears to have been paid to the preparation of the toxin supplied for use in the carrying out of the Schick test, with the result that, in a considerable number of instances, no result whatever has followed on the operation, although there was reason for believing that not all the individuals tested were immune to diphtheria. On the other hand, in a certain number of cases, an unnecessarily severe reaction has been produced.

From these considerations it would obviously be of importance, before the test could be recommended for adoption on a large scale, practically as a routine method for the purpose of estimating the presence or absence of immunity to attack by diphtheria, that arrangements, if necessary under Government

auspices, should be made for the provision of a reliable standard toxin which should always be available for distribution, and with which should be issued explicit directions for its storage, dilution, and use.

For the purposes of our investigation at Southmead Infirmary, at the Headquarters Homes, and at the Downend Cottage Homes—after the first few preliminary tests which for various reasons we regarded as not entirely satisfactory—we have made use of a toxin prepared by Dr. O'Brien, of the Wellcome Research Laboratories, who has had extensive experience of the work necessary in the preparation of a reliable product.

It may, perhaps, be mentioned that the amount of toxin produced as the result of culture of the diphtheria bacillus in liquid media is apt to vary considerably, in consequence probably of minute variations in the composition of the culture fluid, with the result that sometimes large quantities of the material may have to be rejected on account of failure to obtain the required degree of potency. But demonstration has been recently afforded that the addition to the standard nutrient broth of some "buffer" material may suffice to ensure the production of a greatly enhanced potency of the resulting toxin.

(2) *Correctness of Technique.*—Special care needs to be exercised to ensure that the diluted toxin (0·2 c.c.) is inserted *between* the layers of the skin and not *under* the skin. Before commencing the operation the skin should be washed with alcohol to ensure superficial sterilisation.

The needle of the syringe, preferably of platinum iridium, short-pointed, and of exceptionally fine calibre, should fit accurately to the barrel in order to avoid leakage, and should be as sharp as possible. If a number of tests are to be carried out at one sitting it is well to be provided with sufficient needles to enable a separate one to be used for each operation, so as to save the time necessary for individual sterilisation. These should be at hand in a bath of alcohol, from which they are each removed in turn by means of a sterilised forceps.

In carrying out the little operation, the syringe, with its needle fixed firmly in place, is held nearly parallel with the skin, *within* the substance of which it is carefully passed for a distance of about half an inch. This should be done in such a way that the bevel of the needle is uppermost, as this, which can be seen through the upper layers of the skin, will form a guide as to the correct depth of insertion. Otherwise, when the skin is specially thin and delicate, there will be a tendency either to pass the needle subcutaneously, or, on the other hand, to puncture the surface of the skin from below, for it must be borne in mind that there may be marked individual differences in the thickness of the true skin.

If, by mistake, the needle should be passed subcutaneously, it is better to direct it intradermally *from below*, rather than to withdraw it and begin again.

SCHICK TEST.- Photograph taken at Southmead Infirmary, Bristol, illustrating method of performing the test.

[*To face page* 16.]

Intradermal insertion of the needle having been successfully accomplished, fairly strong pressure on the piston of the syringe is necessary to drive the contained fluid between the layers of the skin, this fact accentuating the tendency to leakage at the junction of needle with syringe if their attachment is not accurate.

After injection the needle should be withdrawn slowly so as to avoid the possibility of any of the injected fluid, while still under pressure, escaping through the point of entry of the needle.

Definite proof of the successful insertion of the toxin is afforded by the appearance, on the surface of the skin around the point to which the extremity of the needle has reached, of a small rounded and whitish-coloured swelling, which, from its appearance, we have been accustomed to term the "button" (*see* photograph). This may persist from several minutes up to half an hour or so, although occasionally it disappears fairly rapidly.

Not infrequently also an urticarial condition of the skin develops for a varying distance around the needle-track within a few minutes after the inoculation. The period during which this condition persists is also extremely variable, extending from a few minutes to rarely as long as a couple of days afterwards. But it appears to bear no relation to the ultimate reaction to the test, positive or otherwise; and is probably to be regarded as a form of dermographia, and so, distinct from the so-called pseudo (protein) reaction.

The best *position* at which to make the injection is on the flexor surface of the forearm at about its widest part, care being taken to avoid any small vein.

A *control* injection with a similar dose of toxin solution which, however, has been previously heated to a temperature of 75° C. for 10 minutes should be made at the same time as the test toxin injection, but on the *opposite* arm. We have found in the course of our investigations that unless this precautionary measure is adopted in each instance considerable difficulty is apt to arise as to the correct interpretation of the result of the test.

A simple outfit for the Schick test supplied to practitioners by the Bureau of Laboratories, New York City, comprises a capillary tube containing a little over one minimum lethal dose for a guinea-pig of an undiluted diphtheria toxin; a small rubber bulb for expelling the toxin, similar in design to those supplied with vaccine outfits; and a bottle containing 10 c.c. of sterile normal saline solution. When the toxin is added to the saline a dilution is obtained of which 0·2 c.c. represents $\frac{1}{50}$ of a minimum lethal dose, the amount used in the test.

(3) *Interpretation and Recording of Results.*—If antitoxin is absent from the system or present only in small amounts insufficient for protection from diphtheria, a *positive* reaction

will appear at the site of injection in about 24 hours, becoming gradually more marked within the next two or three days, and reaching its height on the fourth or fifth day. This reaction takes the form of a circumscribed area of redness accompanied by slight infiltration of the skin, which will usually measure from one to two centimeters in diameter. It persists for a week or longer depending on the intensity of the reaction, and leaves, on fading, a brownish area of pigmentation, which at an early stage may exhibit a definite, sometimes quite coarse, desquamation of a whitish colour.

The pigmented area gradually fades, but may persist in some individuals for as long as three or four months.

If an individual is *immune* to diphtheria, a *negative* Schick reaction results, the skin at the site of injection returning to normal after the first few hours, and remaining so. A period of at least 48 hours must elapse before giving a negative report. It has been found that if the blood contains 1/30th of a unit of antitoxin or more per c.c. a negative reaction will be obtained.

Zingher states that the reading of reactions in children under five years of age is quite simple, as the reactions at this age are mostly positive or negative. This may be so in perfectly healthy and normal children, but in our Infirmary cases, the children, who for the most part were of weakly type owing to the effects of more or less chronic disease in various forms, provided numerous exceptions to the rule. In older children, and especially in adults, readings of the results of the Schick reaction are apt, in a considerable proportion of the cases, to be rendered difficult owing to the occurrence of the so-called *pseudo* (*negative*) reaction. This result needs to be carefully distinguished from the positive reaction as it may and does occur in a number of immune individuals and is particularly difficult if the reaction occurs at later ages. It is possibly correlated with susceptibility in the same person to the skin rashes following on the administration of ordinary antitoxin. The pseudo reaction is believed to depend on irritative action produced, in susceptible individuals, by the autolysed proteins (possibly in the form of proteoses) of the diphtheria bacillus, which are necessarily present in small amount in the test solution. The pseudo reaction appears at a much earlier stage than the positive reaction, being usually well-marked after the lapse of about eighteen hours, and reaching its height at the end of twenty-four hours. The area of redness is not definitely circumscribed as in the case of a positive reaction, and tends to merge gradually into the colour of the surrounding skin. Zingher, as the result of his extensive experience, states that in a majority of pseudo negative reactions most of the redness and induration will have faded away by the end of four days, leaving only a small irregular area of pigmentation which may occasionally show a slight central scaling. These pseudo reactions, however, may vary considerably in intensity, and, in some instances, even at the end of four days, may show a well defined area of reddish-brown

pigmentation. It is in such instances that the value of a control test, carried out with heated toxin on the opposite arm, becomes specially apparent, as without such a control it may prove exceptionally difficult to arrive at an accurate determination of the true nature of the reaction obtained. In the presence of a control, however, a correct reading is comparatively simple, seeing that while with a pseudo reaction similar appearances will be afforded both on the area of the test injection as well as on that of the control, in the case of a positive reaction an area of typical redness at the site of the test injection will be in marked contrast with the absence of reaction on the opposite (control) arm. This control test with heated toxin is therefore of the utmost value as affording a means of definitely identifying the character of the reactions obtained.

A certain proportion of susceptible individuals (5·3 per cent. in the case of our own observations—*see* Table I.) may show a *combined* or *pseudo-positive* reaction, representing a combination of a positive and pseudo reaction. In this event the true nature of the reaction should, in our experience at Bristol, be capable of identification by the end of the fourth day, a well-defined positive reaction at the site of the test then contrasting with a partly faded pseudo reaction at the site of the control injection.

We do not think that, in any instance, a definite opinion as to the true classification of a reaction can be safely expressed before the *third* day.

As, according the Zingher, among adults pseudo reactions are two or three times as numerous as positives, the importance of possessing a simple and satisfactory method for their definite identification will be self-evident.

Details of the following three cases illustrate certain points of interest.

No. 5.

Schick test positive. Klebs - Loeffler bacillus present in throat. Francis P———, æt. 3 years. Admitted from Eastville, September 20th, 1920.

January 25th, 1921.—Swab taken from throat; positive. No antitoxin given.

January 26th.—Schick test, no control. Two hours after injection intensely red raised patch appeared.

February 6th.—Firm raised surface with desquamating brownish-purple centre and red margin.

March 5th.—Brownish stain still present.

March 26th.—Faint stain still apparent.

No. 7.

Schick test during attack of diphtheria; negative. Minnie A———, æt. 10 years. Admitted from City of Bristol, October 30th, 1920.

February 28th.—Onset of diphtheria.

March 1st.—Schick test, no control; 1 minim leak. Nose = Hofmann.

March 2nd.—Slight tumefaction of skin over area of Schick test; *no* redness.

March 3rd.—Nil.

TABLE I.

Schick Test.

Bristol. (Southmead Infirmary Headquarters, Downend Homes and Royal Infirmary.)					Zingher, New York.	Monsall Fever Hospital, Manchester.	Edinburgh City Hospital.
Age.	Total.	Positive (including Combined).	Negative (including Pseudo).	Percentage Positive (including Combined), 132 cases.	Percentage Positive, 1,200 cases.	Percentage Positive, 213 cases at Zingher's Age Groups.	Percentage Positive, 500 cases, Scarlet Fever Patients only. 500 cases.
—	—	—	—	Toxin (O'Brien).	—	Toxin (O'Brien).	Toxin (O'Brien).
6 months to 12 months	12	2	10	16·7	50		
1 year to 2 years -	5	1	4	20·0	68	50	100*
2 years to 4 years -	11	4	7	36·4	66	51	78
4 years to 6 years -	24	4	20	16·7	53	46·5	59
6 years to 8 years -	15	2	13	13·3	37	39	58
8 years to 15 years -	45	9	36	20·0	28	36	56
15 years and over -	20	3	17	15·0	24·5	19	37·5
Totals - -	132	25	107	18·9	43·3	38	—

* This figure is also given—not only for the period 1–2 years, but for a further period of 2–5 years, for scarlet fever patients, by Dr. Gladys Ward (B.M.J., June 25th, 1921, p. 928). She refers to Zingher's suggestion that there may be a destruction of the natural diphtheria anti-toxin during an attack of scarlet fever, and to that of Von Behring, that there is a temporary loss of natural immunity to diphtheria during the acute febrile stages of this disease.

March 5th.—Patch on tonsil and slight nasal discharge. Child had pronounced clinical symptoms; rash after injection of anti-toxin (8,000 units).

March 8th.—Throat positive.

No. 47.

Schick test after attack of diphtheria. Long persisting pseudo. Lilian B———, æt. 10 years.

January 31st.—Onset of diphtheria. Severe anti-toxin rash followed injection of 8,000 units.

March 4th.—Schick test, with control.

March 5th.—Right and left arms *both* show red rash shading off into surrounding skin.

March 16th.—Right and left arms both desquamating. Pseudo reaction has thus persisted for over 12 days. It may be noted that all the members of this family, seven in number, show signs of congenital syphilis, that five of them have been under treatment for diphtheria in Southmead Infirmary, and that most of them show intolerance of anti-toxin. In two other members of this family (Nos. 49 and 56), a pseudo reaction also persisted for over 12 days. Two others who had not previously suffered from diphtheria (Nos. 102 and 103) gave a *combined* or pseudo + positive reaction.

Summary of Bristol Cases.

In 57 cases, of ages ranging from four to ten years, the results of the Schick test were as follows:—

Definitely positive	6	9 Positive.
Combined	3	
Definitely negative	31	48 Negative.
Pseudo	17	

The considerable preponderance of negatives shown in the tabular statement on p. 20, is doubtless owing to the fact that many of the children had passed through an attack of diphtheria previously.

III.—ACTIVE IMMUNISATION AGAINST DIPHTHERIA.

The essential corollary to the performance of the Schick test is the active immunisation of all those affording a positive reaction to the test by the method of inoculation with solutions of standard toxin-antitoxin. The development of a lasting active immunity may subsequently be tested by repeating the Schick test on one or more occasions, after such intervals of time as may be considered desirable.

This method for securing active immunisation by the use of diphtheria toxin-antitoxin was first proposed by Von Behring in 1913, about the same time that Schick published his investigations, but unfortunately he did not give exact details of his methods for the preparation of the necessary material. Since that date investigations on the most extensive scale have been carried out in the laboratories of the New York City Department of Health which have resulted in the production of a standard toxin-antitoxin mixture of such a strength that 5 c.c. injected into a guinea-pig, while failing to cause rapid death of the animal, will produce a local induration at the site of injection followed by a late paralysis. With 1 c.c. doses of a toxin-antitoxin mixture of this degree of potency given subcutaneously, and subsequently twice repeated at intervals of seven days, Park and Zingher found that active immunity could be induced in

over 95 per cent. of susceptible individuals, which had been found to persist down to the time of writing (January 1921)—a period of five years. As indicated, a few people (about 5 per cent.) appear to be refractory to active immunisation in the first instance, but if such individuals are discovered, as the result of a further series of Schick tests, to be still susceptible, it will usually be found that an active immunity will be secured by a second course of toxin-antitoxin inoculations given three to six months later.

In view of the high morbidity and mortality from diphtheria of children under five years old, active immunisation of as many children as possible between the ages of six months and two years especially, would seem to be desirable. *Under* the age of six months, however, no effect *quâ* immunisation is likely to be produced. In the case of adults, expecially those giving strong pseudo-reactions, it is important that they should be warned of the risk of more or less severe constitutional disturbances following on toxin-antitoxin inoculations.

At the Southmead Infirmary inoculation with toxin-antitoxin solution was only carried out on a comparatively small number of individuals. The dosage of the solution available required preliminary study and doses considerably less in amount (about $\frac{1}{5}$ c.c.) than the 1 c.c. advocated for the first inoculation by American investigators, were employed. Even with these supposedly ultra-minimal doses the reactions obtained as the result of inoculation of three, at any rate, of the comparatively weakly children at Southmead, and especially in the case of the only one of the nurses to be inoculated, were decidedly severe.

A further reason militating against extension of the work was that by the time we were in a position to commence operations, the greater number of children in the institution had already contracted diphtheria, though in most instances the attack was mild in character. But opportunity for investigation of the value of the method was afforded when two infants contracted the disease in a small ward to which a number of children who, on "swabbing," had given negative results, had been temporarily removed for purposes of isolation. The type of disease in this instance was exceptionally severe, and both children died a few days later. Immediately the disease was recognised in the case of the two infants referred to, these were warded elsewhere for observation and treatment; while ten out of twelve of the remainder were at once inoculated by Dr. Nixon with small doses (3 minims each) of toxin-antitoxin solution, a second inoculation, also 3 minims in amount, being subsequently given to all twelve children. Only one of them subsequently contracted the disease. In this instance only *one* inoculation had been given.

Since this report was drafted further experience has been gained in connection with the occurrence of diphtheria at the Mitcham schools of the Holborn Guardians. All the children in these institutions—a total of 329—ranging in age from three to fourteen years have been submitted to the Schick test on one or

more occasions. Of these, the 98 who afforded a positive reaction have been immunised by means of at least three separate inoculations of toxin-antitoxin at intervals of 4 to 7 days in doses of 0·05 c.c., 0·25 c.c. and 1 c.c. The latter dose has moreover been repeated in certain instances on one or more subsequent occasions.

The result of these inoculations has been quite satisfactory. In regard to reactions, in only three of the 98 children inoculated was the reaction sufficiently severe to render it desirable to confine them to bed for 24 hours subsequently. Of these three, one was found to have been suffering before the inoculation from gastric pain following a dinner of pork, which subsequently induced an attack of vomiting. The temperature of the second child mounted to 102·4° F. after the first dose of 0·05 c.c., but no appreciable reaction occurred after subsequent doses of 0·01 c.c., 0·05 c.c., 1 c.c., 1 c.c. and 1 c.c. The third child suffered from a moderately severe local reaction for two days. Of eight adults inoculated with doses of 0·01 c.c., 0·05 c.c., 1 c.c., 1 c.c. and 1 c.c., none were off duty at any time, although one suffered with malaise and soreness of the arm for a couple of days.

IV.—OBSERVATIONS ON DIPHTHERIA "CARRIERS."

The point of outstanding difficulty in connection with prevention of diphtheria, more particularly in this country, is that of determining the place which measures against "carriers" of the specific micro-organisms should occupy in preventive work, and in what these measures should consist.

It is, of course, now matter of common knowledge that certain individuals may harbour the bacillus, or at any rate an organism in all respects morphologically indistinguishable from the diphtheria bacillus, in throat, nose, or ears, for weeks or months after apparent complete recovery from the disease. In addition, similar organisms have frequently been isolated from swabs taken from individuals who, so far as is known, have never suffered attack by the disease, although they may not improbably be found to have been in more or less close contact, in school or elsewhere, with cases of the disease.

Consequently diphtheria carriers have come to be classified under the two headings of :—

(*a*) Convalescent carriers;
(*b*) Contact carriers;

the former class including those individuals who, having recovered from an attack of diphtheria, so far as clinical symptoms of the disease are concerned, nevertheless still continue to harbour the Klebs-Loeffler bacillus in their throat, nose or ears, as evidenced by its recovery by appropriate cultural methods from swabs.

"Contact carriers" on the other hand comprise instances, often much more numerous than the class of "convalescent

carriers," which afford "positive" results on swabbing and culture, but in which no history of a previous attack of diphtheria, so far as clinical symptoms are concerned, can be obtained.

Presumably original infection of a series of these cases has come about through association with a clincial case of the disease, or with a "convalescent carrier." Once the series is established, infection may also, presumably, be passed from contact carriers to other persons who, in turn, become contact carriers only. In contrast to "convalescent carriers," "contact carriers," when otherwise in good health, not infrequently become normal in a few days, as evidenced by the fact that swabbing no longer affords a positive result on culture.

As with "convalescent carriers," however, in a certain number of "contact carriers" the bacillus may persist for an indefinite period, so that both classes have to be further classified as "transient" or "chronic." In this connection it may be mentioned that, as regards convalescents from actual diphtheria, according to Dr. Weaver (*Journal of the American Medical Association*, March 26th, 1921), 83·2 per cent. of cases admitted to the Durand Hospital, Chicago, in the period 1913–1920, gave three successive negatives to cultural examination four weeks after onset of the disease. Among the remainder ("convalescent carriers") persistent positive results from pharyngeal material are said to have been associated with abnormal tonsils, and persistent positives from nasal material with adenoids and chronic rhinitis.

Hartley and Martin (*Proc. Royal Society of Med.; Sect. Epidem. and State Med.*, July 1920), utilizing data obtained by them as the outcome of 3,070 observations in 457 cases of the disease, were enabled to reduce to a mathematical formula the rate at which the diphtheria bacillus disappears from the throats of convalescents. They also demonstrated mathematically how the results obtained by different observers depend on the standard used. Their own criterion was the obtaining of three successive negative cultures at weekly intervals, for which an average stay of 45 days in hospital was required. If the standard was lowered so that only two successive negatives were required the period of stay was reduced to 34 days, while with one negative only the necessary period was 21 days. These figures, however, do not apply in the case of patients with abnormal throats, as they found that convalescents with abnormally large tonsils with deep crypts are prone to become stubborn carriers. Further they support the contention of Pegler (1905), Sears (1919) and others that the best treatment in these cases consists in radical enucleation of the tonsils.

As regards the duration of the carrier condition in contact cases, I may here refer to the result of some examinations which were made in connection with the Southmead Infirmary enquiry at the Downend Schools near Bristol. Evidence of diphtheria in these schools led to extensive and systematic swabbing under-

taken by the Medical Officer of Health of the Warmley Rural District, Dr. Aubrey, the swabs and cultures being examined by Professor Walker Hall, or by Dr. Scott in the Ministry's laboratory. The total number of children tested was 427. Nine children were found to be carriers of diphtheria bacilli—six in the throat, two in the nose and one in both throat and nose. The only known case of diphtheria in the school had been identified and isolated on February 16th, 1921; the nine contact carriers were identified from swabs taken at the end of March, and, as the result of numerous examinations of additional swabs, the carrier condition was found to have disappeared in all nine cases by 25th April.

All the available evidence goes to show that the virulence of the organisms recoverable from "carriers" of one or the other kind (and so their importance as regards potential spread of the disease) varies enormously, some strains being, so far as in the light of our present knowledge it is possible to judge, completely avirulent, a condition most frequently observed in the case of "contact carriers." The question whether and under what circumstances, and to what extent, these apparently harmless strains are capable of regaining virulence requires further study. American observers appear unanimous in the opinion that once virulence is lost it is never regained.

As a matter of fact the number of "carriers" discovered in connection with any particular outbreak of diphtheria, or even in any given population at the time not known to be invaded by the disease, will be found to depend to some extent on the energy and skill devoted to the search.* Consequently it is a moot point whether a positive bacteriological finding, in absence of clinical symptoms, is sufficient evidence on which, for instance, to take any action which entails the recognition of the case as infective. Routine removal of such cases to hospital is to be deprecated. It is doubtful whether, in such cases, there is justification for so stretching the interpretation of the term "diphtheria" as to permit the carrier being formally notified as diphtheria under the Notification Acts. The latter practice is followed in some districts, but leads to confusing results. An extreme case is recorded by Dr. Hutchinson, who, when investigating an outbreak of diphtheria in a large institution near London, found that of 107 notified cases, the diagnosis, in no less than 100 of these, had been based on bacteriological grounds alone. In this instance the main object of notification was defeated, as it was obviously impossible to isolate so large a number of cases.

The only test capable of affording reliable evidence as to the virulent nature or otherwise of any particular strain of organism is probably *the experimental* one of *animal inoculation*, details as to the technique of which will be found in Appendix 2 of this

* Eyre isolated the Klebs-Loeffler bacillus from the throats of nearly 7 per cent. of a presumably healthy population.

report. At present, however, facilities for the carrying out of such work are not readily available in this country.

Results of importance as regards the practical significance of the carrier state and the question how, from the point of view of the community, diphtheria carriers should be dealt with have recently been published by Guthrie, Galien and Moss (*Bulletin Johns Hopkins Hospital, Baltimore*, 1920, xxxi, 388–403). They state that in February, 1912, a single throat-swab from each of 800 children attending one of the public schools in Baltimore revealed diphtheria bacilli in 85 children, or 10·6 per cent.; a re-examination of the same 800 children three months later gave positive cultures in 69, or 8·6 per cent.; and the number of children yielding positive cultures at either one or the other examination was 144, or 18 per cent. Virulence tests on guinea-pigs (a positive result being reported when death occurred with characteristic lesions within four days) were carried out with diphtheria bacilli from 99 cases, of which 9 were found to harbour virulent bacilli. From further swabbing of some of these 800 children, 15 more carriers were discovered, bringing the total up to 159. Only 11 of these 159 carriers gave a history of having had diphtheria, and none within the previous three years; while under observation none of them subsequently developed diphtheria. Fourteen of the carriers gave a history of exposure to diphtheria at periods varying from one to twelve years previously. Careful inquiry failed to find any example of the disease arising among the contacts of the 159 carriers. In order to determine how long diphtheria bacilli persist in the throats of persons with positive cultures, but without clinical evidence of the disease, 50 of the carriers mentioned above were examined at intervals of two weeks for three months: at the end of this period six only were positive.

With the object of throwing light on the question whether or not diphtheria bacilli in the throat can undergo a change in virulence—that is to say, whether non-virulent bacilli become virulent—an experiment was performed on five healthy persons proved to be free from diphtheria bacilli by daily cultures over a period of two weeks; their throats were then inoculated with a pure culture of non-virulent bacilli, and, after that, daily swabs were examined for some weeks, then swabs were taken at intervals of a few days for three months, and subsequently at longer intervals for about fifteen months; three of these five individuals became carriers, but none ever showed virulent bacilli or suffered from symptoms referable to the diphtheria bacilli in their throats. A series of observations on the cultural and staining reactions showed that virulent and non-virulent diphtheria bacilli are exactly alike, and can be distinguished only by the toxin-producing power possessed by the virulent bacilli as shown by the guinea-pig test. The other members of the diphtheria group are readily differentiated from the diphtheria bacilli, and are without any pathogenic significance.

The conclusions which appear to be deducible from these observations may be briefly summarised as follows :—the diphtheria bacilli in a majority of otherwise healthy carriers are non-virulent ; non-virulent bacilli cannot cause diphtheria : there is no proof that non-virulent bacilli are a menace to others or to the community at large, and interference with their liberty is unwarranted. It may be advisable to isolate carriers until the question of virulence of their bacilli has been decided, but, if the culture proves non-virulent, further detention of the carrier is unjustifiable.

No doubt time and expense are entailed by the guinea-pig test, and a simpler and less expensive one would be advantageous : but this drawback is less serious than the economic loss and inconvenience incurred by needless isolation of the carrier of non-virulent bacilli.

Treatment of Carriers.

In the event of a " carrier " being found to harbour a virulent strain of organism it would seem, in any case, undesirable that, if a child, it should return to school, unless indeed it is feasible to arrange for its admission, under special supervision, to an open-air school. Under such conditions the health of the child would be likely to benefit, while danger of transference of infection would be reduced to the minimum.

Unfortunately, thus far, no certain method has been devised for the curative treatment of carrier cases, especially those of long standing, so that further investigation of the subject in all its bearings is obviously desirable. Meanwhile there is a wide choice among the various methods, bacteriological, chemical, pharmaceutical and surgical, that have been suggested from time to time. Dr. Park, in common with many other observers to whom reference has previously been made, advises the removal of hypertrophic lymphatic tissue (enucleation of tonsils, removal of adenoids), which, he says, aids the disappearance of the bacilli in chronic carriers. Obviously, however, no operative measure of this nature should be undertaken unless and until the naso-pharynx and throat are otherwise in a healthy condition, and the general health of the patient is satisfactory. Arguing from analogy it does not seem probable that " vaccine " methods can be of much service, as, although some immunity may result, this would not necessarily destroy bacteria which are living a saprophytic existence outside the living tissues. If a vaccine is used it should be an autogenous one. Hewlett has recently reported successful results in a number of cases from the repeated use by subcutaneous inoculation of a diphtheria *endotoxin* at intervals of seven to ten days.

Thomson's detoxicated vaccine has been favourably reported on by Fraser and Duncan, who record the successful treatment of three " carrier " cases by this means.

Brownlie, who has employed inoculations of a " stock " bacterial vaccine in the treatment of 50 diphtheria carriers,

reports good results in the majority of his cases. In 44 of the cases, although only three doses were given, the patients were discharged on the eleventh day, two negative cultures having previously been recorded in each instance. No bad effects followed use of the vaccine, which was found to produce well-defined degeneracy in the morphological appearance of the organism in culture, together with its rapid and complete disappearance from the site of invasion.

In conclusion, it is obviously desirable that facilities should be afforded for the fullest investigation of the Schick test, and of the system of immunisation by means of toxin-antitoxin inoculations, with a view especially to deciding on the advantages which might result from its adoption in this country for the protection of school-children and other "community" populations, as also of nurses working in the diphtheria wards of an infectious diseases hospital.

Apart from this, however, experimental determination of the virulence or otherwise of the cultures obtained from "carriers" of the diphtheria bacillus should result in the saving of much time, expense, and administrative labour, by releasing from supposed necessity for treatment, as well as from restrictions as to work, school attendance, &c., numerous individuals who, if recent opinion in this country and abroad is confirmed, may be regarded as in no way constituting a danger to the public health.

S. MONCKTON COPEMAN.

APPENDIX 1.

NEW YORK RECOMMENDATIONS AS TO PRACTICAL APPLICATIONS OF THE SCHICK TEST.

These are summarised by Dr. Zingher (*Monthly Bulletin*, New York State Department of Health, January, 1921) somewhat as follows:—

(*a*) The Schick test should be used in the home where a child has developed diphtheria. By testing the other children and adults the susceptible individuals are found. Each of these should then be injected at once with a prophylactic dose of antitoxin in the usual way to produce an immediate passive immunity. The delay of 48 hours, necessary for the earliest reading of the result of the Schick test, has little danger connected with it, and has the advantage of avoiding the injection of antitoxin into those who do not need it. However, in the case of young children who have been in close contact with the disease, especially if they cannot be observed during the next 48 hours, it will be safer, under certain conditions, to give prophylactic injections of antitoxin at once without waiting for the result of the Schick tests.

(*b*) During an outbreak of diphtheria in institutions and schools, the application of the Schick test will enable one to select the susceptible children, who may be only 20–25 per cent. of the total, and immunise them with antitoxin. It is thus possible rapidly to control an outbreak of diphtheria in an institution or school.

(*c*) The Schick test is of great value as a routine procedure in infectious disease hospitals and in various other hospitals, institutions and homes caring for children, including orphan and infant asylums, day nurseries, public and private schools.

Children over two years of age who give negative Schick reactions will continue to give such reactions over a period of years if the same technique and the same standard dilution of toxin is used in making the test. It seems, therefore, that such natural immunity persists for a long period of years, and possibly for life. The fact that the negative Schick reaction in these naturally immune individuals indicates a long and persistent immunity adds great value to the use of the test in homes, institutions, &c.

(*e*) In routine prophylactic work in diphtheria, when there is no immediate danger from the disease, the Schick test should be employed in conjunction with active immunisation with toxin-antitoxin. Subsequently it is advisable that those who have received the immunising injections of toxin-antitoxin should be re-tested by means of the Schick test after an interval of about six months in order to obtain information as to whether development of an active immunity has been obtained.

APPENDIX 2.

METHODS OF CARRYING OUT EXPERIMENTAL TESTS FOR VIRULENCE OF DIPHTHERIA ORGANISMS.

1. *Subcutaneous Method.*—In carrying out the ordinary *subcutaneous test* for virulence on the guinea-pig, two animals are required—one as a control—which should each weigh about 250 grms. One is injected preferably with 1 c.c. of an ascitic broth culture (incubated for 48 hours); the second guinea-pig is injected with the same amount of culture + 50 to 100 units of diphtheria antitoxin. If the first pig dies within three to

four days, with local œdema at the site of inoculation, and showing P.M. typical engorgement of the supra-renal glands, while the control pig survives, proof as to the virulence of the culture will have been afforded.

Using this method, the number of guinea-pigs required will, obviously, always correspond with the number of tests to be carried out + an equal number of animals as controls.

2. *Intra-cutaneous Method.*—The expense of the work, especially when a large number of tests have to be carried out, will be considerably reduced by employing the *intra-cutaneous* method of Zingher and Soletsky (*Jour. Inf. Dis.* 1915, p. 454), which, though it requires some experience in judging as to the skin lesions produced, has the advantage that from four to six cultures can be tested with a couple of guinea-pigs only.

The intra-cutaneous test is carried out as follows: Two guinea-pigs, weighing about 350 grms., are used for the testing of from four to six different strains. One pig, as a control, receives 0·5 c.c. of antitoxin (about 500 units per c.c.) intracardially at the time of the tests, or intra-peritoneally 24 hours before. The intracardial injection is the better as it produces a complete inhibition of the local action of virulent bacteria in the control injections. The hair on the abdominal surface of each pig is removed, either by the application of a paste made of barium sulphide, or preferably by pulling the hair out. This can be done easily with probably less pain than is associated with the prolonged irritation which, at times, follows the application of the depilatory. For the bacterial emulsion, a fresh 24-hour growth from an ordinary Loeffler slant, or a glucose ascitic slant of equal size, is suspended in 20 c.c. of normal salt solution. It is important that the growth be no more than 24 hours old, since many of the bacteria die if the culture is kept for 48 hours or longer in the incubator. . . . Suspensions of the cultures to be tested having been prepared in the way described, 0·15 c.c. of each is injected intra-cutaneously into both guinea-pigs. The abdominal surface is divided into four or six areas, in accordance with the size of the guinea-pig, and the injections are made as far apart as possible in order to avoid a fusion of the lesions. Four strains can be tested on a medium-sized guinea-pig, and six on a larger one, without the danger of overlapping. A 0·5 c.c. or 1 c.c. Record syringe, with a very fine steel or platinum-iridium needle, is suitable for the injection. If the injections have been made properly, a circumscribed elevation appears, which persists for a few minutes.

The results of the tests are noted in 24, 48 and 72 hours. Virulent strains produce a definitely circumscribed local inflammatory lesion, which shows a superficial necrosis in from 48 to 72 hours. In the control pig the skin remains normal, if the injections have been accurately carried out. With non-virulent strains, no lesion will be found in either control or test animal.

In this way four cultures can be tested on two animals, as compared with eight animals in the older way. The control animal may be used again within a week for another set of tests without a further injection of antitoxin. By the use of larger guinea-pigs, on which six tests can be made, 10 or 12 can be saved, a considerable advantage when a large number of strains is to be tested.

Dr. R. A. O'Brien and his colleagues of the Wellcome Research Laboratories have recently elaborated methods which, while retaining complete efficiency of the test have, at the same time, been successful in reducing the expense to a minimum, seeing that 10 to 15, or even more, tests can be carried out on a single guinea-pig, while none of the animals employed for the purpose of the investigations are necessarily sacrificed. Sufficient area for so large a number of tests is secured by shaving practically the whole space between the fore and hind limbs on either side of the animal, the intra-cutaneous insertions of the various cultures being made at intervals of about an inch from one another on the skin surface thus laid bare.

In addition, there is made on each animal an extra insertion of " Park No. 8 " test toxin for purposes of comparison. The control guinea-pig, prior to inoculation, receives an injection of 500 units of antitoxin, while the other animal also receives an injection of antitoxin of less amount (125 units) about five hours after the last intra-dermal test inoculation. This delayed treatment with a comparatively small dose of antitoxin does not in any way invalidate the development of the cutaneous reaction as the toxin has had time to " fix " itself in the epidermal cells, although it suffices to prevent the fatal result which would otherwise ensue.

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